EXHIBIT 21

Cancer
Epidemiology,
Biomarkers
& Prevention

Douching, Talc Use, and Risk for Ovarian Cancer and Conditions Related to Genital Tract Inflammation

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Abstract

Background: Douching is associated with disorders involving genital tract inflammation and genital talc use with epithelial ovarian cancer (EOC), but their joint effects are infrequently considered.

Methods: From 2,040 cases of EOC and 2,100 controls enrolled in eastern Massachusetts and New Hampshire, we used unconditional logistic regression to estimate risk for EOC associated with douching and/or talc use. In subsets of cases and controls, we also collected information about pelvic inflammatory disease (PID), ectopic pregnancy, and cervical neoplasia to estimate risk for these events from douching and/or talc use.

Results: The adjusted OR and 95% confidence interval (CI) for all EOC was 0.94 (0.76–1.16) in women who douched but never used talc and 1.28 (1.09–1.51) in women who used talc but never douched. Compared with women who never regularly douched or used talc, ORs (95% CIs) were 0.83 (0.52–1.33) for women who both used talc and homemade douches and 1.53 (1.11–2.10) for women who both used talc and store-bought douches. Cases who both douched and used talc were more likely to have had PID compared with cases who had used neither [OR = 5.03 (95% CI, 1.61–15.7)].

Conclusions: Douching is not an independent risk factor for ovarian cancer, but the combination of talc use and store-bought douches may modestly increase the risk for EOC beyond that for talc use alone.

Impact: The joint effect of talc use and douching, especially with commercial products, should be considered in evaluating risks associated with disorders involving genital tract inflammation or EOC.

Introduction

Two relatively common feminine hygienic practices include vaginal douching and use of talc powders or sprays in the genital area. From a National Survey of U.S. women of reproductive age conducted in the late 1980s (1), 37% reported regular douching. A nearly identical proportion reported using talc in their genital area from a survey of older women conducted in the Northwest around the same time period (2). Reasons reported by women who douche include the desire for cleanliness and fresh smell (3), with use often around the time of menses or sexual activity. Because women who douche are also more likely to use talc, the latter group may have similar motivations (2). Epidemiologic factors associated with both practices include Black ethnicity, high body mass index (BMI), married status, and smoking (2, 3).

That a substantial proportion of women in the United States douche or use talc suggests these practices are widely perceived to be innocuous. However, epidemiologic studies suggest both may adversely affect reproductive health. Douching has been associated with pelvic inflammatory disease, ectopic pregnancy, cervical neoplasia, and bacterial and fungal vaginosis (4–9), and genital use of talc has been associated with increased risk of ovarian cancer (10). A recent study suggested that douching may also be associated with ovarian cancer (11); but whether talc use is associated with other adverse reproductive events, like pelvic inflammatory disease (PID) or cervical neoplasia linked to douching, has not been systematically investigated. A key issue in these studies is to what extent the factors that predispose women to douche or use talc use may also be independent risk factors for ovarian cancer or other adverse reproductive events, that is, how well has confounding been controlled for in the studies?

Here, we use data from a large case–control study of ovarian cancer conducted in New England between 1992 and 2008 with uniform data collected on talc use and douching. We estimated risk for ovarian cancer and other adverse reproductive outcomes associated with douching or genital talc use taking into consideration those factors that may influence why women choose to douche or use talc genitally.

Material and Methods

Data came from the three enrollment phases of the New England–based Case Control Study (phase I 1992–1997; phase II: 1998–2002; and phase III: 2003–2008). Details regarding enrollment are described elsewhere (10). Briefly, 3,957 women residing in Eastern Massachusetts and New Hampshire diagnosed with ovarian cancer between ages 18 and 80 were identified through tumor boards and registries. A total of 874 cases had either died or were ineligible because they had moved outside the study area, did not have a working telephone number, or had a

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non-ovarian primary tumor. Of the remaining 3,083 cases, 2,203 (71%) were enrolled. After excluding 128 non-epithelial and 35 mixed mesodermal tumors, 2,040 cases with epithelial tumors of ovarian, primary peritoneal, and fallopian tube origin, including borderline malignancies [henceforth, epithelial ovarian cancer (EOC)] were available for analysis.

Controls were identified through random digit dialing, driver license lists, and town-resident lists. Between 1992 and 1997, 420 (72%) women identified through random digit dialing and 102 (51%) women identified through lists agreed to participate. From 1998 to 2008, 4,366 potential controls were identified using the lists, of whom 1,426 (33%) were ineligible because they had died, moved, were too ill to participate, did not have a working phone, did not speak English, or had surgical removal of ovaries. Of eligible controls, 1,362 (46%) declined to participate by phone or via "opt-out" postcard and 1,578 (54%) were enrolled (2,100 total). Controls were frequency matched to cases by 5-year age groups and region of residence.

Exposure and outcome assessment

Subjects were interviewed in-person about potential EOC risk factors that occurred more than 1 year before diagnosis for cases and 1 year before date of interview for controls. Subjects were asked whether they "regularly" or "at least monthly" applied powder to: the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital–rectal area. Additional details included type of powder, age begun, years used, and applications per month. Lifetime exposure was estimated by multiplying the frequency of applications per month by months used. This was divided by 360 (i.e., daily use coded as 30/month) to yield talc-years. To create categorical variables for talc-years, we chose cut-off points based on quartiles for exposed controls and rounded to the nearest integer. Participants were asked whether they ever douched "regularly" and if they did, they were asked to provide the brand name or type of douches used, the age they began using them, and the total years used. We classified type of douche into any use of store-bought douche or homemade douches only. Women who used both store-bought and home-made douches (14 cases and seven controls) and women who said they used deodorant vaginal suppositories (two cases and two controls) were counted with those who used store-bought douches. In addition, we classified age at first use into three categories, <20, 20–29, and ≥30, and years of use into quartiles based on the control distribution of use.

Subjects were also asked about the occurrence of PID, ectopic pregnancy, and cervical neoplasia, the latter based upon either a history of cervical cancer, intraepithelial neoplasia, or abnormal pap smear that required hysterectomy, conization, or a loop electrosurgical excision procedure. PID was assessed only in the last phase of the study, and cervical procedures were recorded only for study phases II–III. Risks for PID, ectopic pregnancy, and cervical neoplasia associated with talc use or douching were examined individually in EOC cases and controls separately.

Pathology reports were collected for all cases and reviewed by a gynecologic pathologist (W.R. Welch). Tumors were classified by behavior and histology (serous borderline, serous invasive, mucinous, endometrioid, clear cell, and other). Undifferentiated and transitional cell carcinomas, fallopian tube primaries, and primary peritoneal tumors were counted as serous. Mixed epithelial, malignant Brenner, and unspecified epithelial tumors were classified as other.

Statistical analysis

χ^2 tests were used to compare characteristics of cases and controls who did or did not douche or use talc in the genital area. We used unconditional logistic regression to estimate ORs and 95% confidence intervals (CI) for EOC. We examined the association between douching and EOC, stratified by genital talc use and the association between talc use and EOC, stratified by douching. We also examined these associations within histologic types of EOC. In addition, we modeled risk of adverse reproductive outcomes (PID, ectopic pregnancy, and cervical neoplasia) separately among cases and controls. Models were adjusted for the study matching factors (age, study center, and phase) and potential confounders including parity (continuous), oral contraceptive use (never, <23 months, 23–49 months, 50–96 months, and >96 months), BMI (continuous), race (white and non-white), diaphragm use (never and ever), spermicide use (never and ever), menopausal status (pre and post), marital status (never and ever married), smoking (never, former, and current), days of menstrual flow (≤5 and >5) and age at menarche (continuous), and tubal sterilization (yes and no). Tests for trend for duration of douching and talc-years were based on the Wald statistic using continuous variables weighted by category midpoints with zero assigned as the exposure for nonusers. Likelihood ratio tests comparing models with and without interaction terms were used to test for effect modification. Because exposure data were censored by date of diagnosis of ovarian cancer and not on the date of the adverse events, dose-response and trend analyses were not performed for those outcomes. Records with missing data for the exposure of interest were excluded from logistic regression models. Among model covariates, data were missing for BMI ($n = 11$), age at menarche ($n = 16$), and race ($n = 2$). Missing data points were assigned to the most common or median value for each variable to allow records with missing data to be included in multivariable models. Analyses were performed using SAS v9.4 (SAS Institute).

Ethical approval

Institutional review boards approved the study. All participants provided written informed consent.

Results

Several factors associated with the likelihood of douching were also associated with likelihood of using talc genitally and were seen in both cases and controls. Women more likely to engage in both practices were: older, postmenopausal, heavier, and married (Table 1). Women who douched were more likely to be smokers, parous, and have had a tubal ligation and less likely to have used oral contraceptives. Cases who used a diaphragm or had a tubal ligation and controls who used spermicides were more likely to have used talc. Among cases, douching and talc use varied by age at menarche but without any apparent trend for the practices to be associated with an earlier or later menarche. Among controls, those who reported more than 5 days of flow were more likely to douche than women with fewer days of flow. Accordingly, in subsequent tables, we adjusted for these factors in looking at risk for EOC or adverse reproductive outcomes.

Overall risk of EOC was not elevated for women who douched, compared with those who did not, OR (95% CI) = 0.98 (0.83–1.17; Table 2). The ORs for douching in relation to EOC were similar among women who used genital talc, OR = 1.03 (95% CI,

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Table 1. Characteristics of cases and controls by douching and genital talc use

| | Douching | | | | | | Genital talc use | | | | | |
| | Cases | | | Controls | | | Cases | | | Controls | | |
	No	Yes	P	No	Yes	P	No	Yes	P	No	Yes	P
Age, years												
<50	699 (86.3%)	111 (13.7%)	0.001	744 (89.1%)	91 (10.9%)	<0.0001	599 (74.0%)	211 (26.0%)	<0.0001	670 (80.2%)	165 (19.8%)	<0.0001
50–64	683 (80.4%)	166 (19.6%)		705 (80.4%)	172 (19.6%)		541 (63.7%)	308 (36.3%)		599 (68.3%)	278 (31.7%)	
≥65	301 (79.0%)	80 (21.0%)		289 (74.5%)	99 (25.5%)		258 (67.7%)	123 (32.3%)		282 (72.7%)	106 (27.3%)	
Menopausal status												
Pre	776 (86.3%)	123 (13.7%)	<0.0001	830 (89.1%)	102 (10.9%)	<0.0001	652 (72.5%)	247 (27.5%)	0.0006	735 (78.9%)	197 (21.1%)	<0.0001
Post	907 (79.5%)	234 (20.5%)		908 (77.7%)	260 (22.3%)		746 (65.4%)	395 (34.6%)		816 (69.9%)	352 (30.1%)	
Center												
MA	1,343 (83.2%)	272 (16.8%)	0.13	1,424 (83.3%)	285 (16.7%)	0.15	1,082 (67.0%)	533 (33.0%)	0.004	1,232 (72.1%)	477 (27.9%)	0.0001
NH	340 (80.0%)	85 (20.0%)		314 (80.3%)	77 (19.7%)		316 (74.4%)	109 (25.6%)		319 (81.6%)	72 (18.4%)	
Study												
Phase I	460 (82.6%)	97 (17.4%)	0.97	419 (80.3%)	103 (19.7%)	0.13	408 (73.2%)	149 (26.8%)	0.01	430 (82.4%)	92 (17.6%)	<0.0001
Phase II	541 (82.2%)	117 (17.8%)		595 (82.5%)	126 (17.5%)		448 (68.1%)	210 (31.9%)		519 (72.0%)	202 (28.0%)	
Phase III	682 (82.7%)	143 (17.3%)		724 (84.5%)	133 (15.5%)		542 (65.7%)	283 (34.3%)		602 (70.2%)	255 (29.8%)	
Race												
White	1,627 (83.1%)	332 (16.9%)	0.005	1,710 (82.9%)	352 (17.1%)	0.13	1,343 (68.6%)	616 (31.4%)	0.97	1,526 (74.0%)	536 (26.0%)	0.25
Non-white[a]	56 (70.9%)	23 (29.1%)		28 (73.7%)	10 (26.3%)		54 (68.4%)	25 (31.6%)		25 (65.8%)	13 (34.2%)	
BMI[b]												
<20	141 (87.6%)	20 (12.4%)	<0.0001	123 (86.0%)	20 (14.0%)	0.0006	124 (77.0%)	37 (23.0%)	0.004	124 (86.7%)	19 (13.3%)	0.0005
20–24.9	745 (86.3%)	118 (13.7%)		794 (85.3%)	137 (14.7%)		608 (70.5%)	255 (29.5%)		692 (74.3%)	239 (25.7%)	
25–29.9	436 (78.4%)	120 (21.6%)		517 (82.3%)	111 (17.7%)		375 (67.4%)	181 (32.6%)		460 (73.2%)	168 (26.8%)	
≥30	359 (78.4%)	99 (21.6%)		296 (76.1%)	93 (23.9%)		289 (63.1%)	169 (36.9%)		267 (68.6%)	122 (31.4%)	
Smoking status												
Never	825 (86.0%)	134 (14.0%)	<0.0001	876 (87.0%)	131 (13.0%)	<0.0001	668 (69.7%)	291 (30.3%)	0.18	759 (75.4%)	248 (24.6%)	0.23
Former	598 (82.3%)	129 (17.7%)		635 (79.6%)	163 (20.4%)		480 (66.0%)	247 (34.0%)		573 (71.8%)	225 (28.2%)	
Current	260 (73.4%)	94 (26.6%)		227 (76.9%)	68 (23.1%)		250 (70.6%)	104 (29.4%)		219 (74.2%)	76 (25.8%)	
Married												
Never	303 (88.9%)	38 (11.1%)	0.0007	175 (90.7%)	18 (9.3%)	0.002	251 (73.6%)	90 (26.4%)	0.03	153 (79.3%)	40 (20.7%)	0.07
Ever	1,380 (81.2%)	319 (18.8%)		1,563 (82.0%)	344 (18.0%)		1,147 (67.5%)	552 (32.5%)		1,398 (73.3%)	509 (26.7%)	
Parity												
Nulliparous	572 (88.1%)	77 (11.9%)	<0.0001	335 (88.6%)	43 (11.4%)	0.0009	454 (70.0%)	195 (30.0%)	0.34	284 (75.1%)	94 (24.9%)	0.53
Parous	1,111 (79.9%)	280 (20.1%)		1,403 (81.5%)	319 (18.5%)		944 (67.9%)	447 (32.1%)		1,267 (73.6%)	455 (26.4%)	
OC use												
Never	786 (80.7%)	188 (19.3%)	0.04	612 (79.9%)	154 (20.1%)	0.008	672 (69.0%)	302 (31.0%)	0.67	559 (73.0%)	207 (27.0%)	0.49
Ever	897 (84.1%)	169 (15.9%)		1,126 (84.4%)	208 (15.6%)		726 (68.1%)	340 (31.9%)		992 (74.4%)	342 (25.6%)	
Tubal ligation												
No	1,471 (83.4%)	292 (16.6%)	0.005	1,406 (83.6%)	275 (16.4%)	0.03	1,222 (69.3%)	541 (30.7%)	0.05	1,241 (73.8%)	440 (26.2%)	0.95
Yes	212 (76.5%)	65 (23.5%)		332 (79.2%)	87 (20.8%)		176 (63.5%)	101 (36.5%)		310 (74.0%)	109 (26.0%)	
Diaphragm												
No	1,208 (82.1%)	264 (17.9%)	0.41	1,190 (82.1%)	259 (17.9%)	0.25	1,031 (70.0%)	441 (30.0%)	0.02	1,079 (74.5%)	370 (25.5%)	0.34
Yes	475 (83.6%)	93 (16.4%)		548 (84.2%)	103 (15.8%)		367 (64.6%)	201 (35.4%)		472 (72.5%)	179 (27.5%)	
Spermicides												
No	1,549 (82.8%)	322 (17.2%)	0.25	1,586 (82.7%)	332 (17.3%)	0.78	1,286 (68.7%)	585 (31.3%)	0.51	1,432 (74.7%)	486 (25.3%)	0.007
Yes	134 (79.3%)	35 (20.7%)		152 (83.5%)	30 (16.5%)		112 (66.3%)	57 (33.7%)		119 (65.4%)	63 (34.6%)	
Amount of flow												
Light/moderate	994 (82.9%)	205 (17.1%)	0.45	1,019 (83.7%)	199 (16.3%)	0.13	838 (69.9%)	361 (30.1%)	0.09	898 (73.7%)	320 (26.3%)	0.98
Moderate heavy/heavy	674 (81.6%)	152 (18.4%)		690 (81.1%)	161 (18.9%)		548 (66.3%)	278 (33.7%)		627 (73.7%)	224 (26.3%)	

(Continued on the following page)

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Table 1. Characteristics of cases and controls by douching and genital talc use (Cont'd)

| | Douching | | | | | | Genital talc use | | | | | |
| | Cases | | | Controls | | | Cases | | | Controls | | |
	No	Yes	P	No	Yes	P	No	Yes	P	No	Yes	P
Age at menarche, years												
<12	347 (80.7%)	83 (19.3%)	0.01	344 (81.3%)	79 (18.7%)	0.65	286 (66.5%)	144 (33.5%)	0.02	311 (73.5%)	112 (26.5%)	0.93
12–13	976 (83.3%)	195 (16.7%)		980 (83.5%)	194 (16.5%)		786 (67.1%)	385 (32.9%)		872 (74.3%)	302 (25.7%)	
14	198 (86.8%)	30 (13.2%)		202 (83.5%)	40 (16.5%)		175 (76.8%)	53 (23.2%)		175 (72.3%)	67 (27.7%)	
>14	154 (75.9%)	49 (24.1%)		205 (81.0%)	48 (19.0%)		145 (71.4%)	58 (28.6%)		186 (73.5%)	67 (26.5%)	
Days of flow												
≤5	1,128 (82.5%)	239 (17.5%)	0.92	1,192 (83.8%)	230 (16.2%)	0.05	935 (68.4%)	432 (31.6%)	0.96	1,033 (72.6%)	389 (27.4%)	0.07
>5	541 (82.3%)	116 (17.7%)		534 (80.3%)	131 (19.7%)		450 (68.5%)	207 (31.5%)		508 (76.4%)	157 (23.6%)	

Abbreviation: OC, oral contraceptive.
a Non-white race includes 58 African American, 64 Hispanic, 46 Asian, and 9 Other race women.
b BMI is missing for two cases and nine controls.

0.77–1.38) and those who did not, OR = 0.94 (95% CI, 0.76–1.16). Excluding women with tubal ligation (rather than adjusting for it) did not materially change these estimates; OR = 0.98 (95% CI, 0.81–1.19) for douching overall, OR = 1.09 (95% CI, 0.79–1.52) for douching and talc, and OR = 0.93 (95% CI, 0.73–1.18) for douching alone. No trends in overall risk for EOC were associated with age-at-first use of douching or years of douching overall or in subgroups of women who used or did not use talc. Risk of EOC overall appeared to be decreased with use of "homemade" douching products OR (95% CI), 0.78 (0.60–1.02) whereas risk was increased with use of "store-bought" products, OR = 1.11 (0.91–1.37), but neither association was statistically significant. This difference was more apparent among women who used talc but did not reach significance in tests for heterogeneity (see Table 2 footnote).

In Table 3, we show the findings for talc use overall and in analyses stratified by douching. Women who used talc had an elevated risk for EOC overall compared with those who did not, OR (95% CI), 1.30 (1.13–1.50). The ORs for talc use in relation to EOC were similar among women who had also regularly douched, OR, 1.32 (95% CI, 0.95–1.82) and those who had not, OR, 1.28 (95% CI, 1.09–1.51). Excluding women with tubal ligation slightly lowered these estimates but did not change their significance; OR, 1.23 (95% CI, 1.05–1.44) for talc use overall, OR, 1.33 (95% CI, 0.92–1.92) for talc and douching, and OR, 1.19 (95% CI, 1.00–1.42) for talc alone. Risks were greater for women who began talc use during their 20s, and this was true regardless of whether the woman also douched. Risk of EOC increased significantly with increasing talc-years and the trend was more apparent in women who did not regularly douche. The ORs associated with ever-use of talc, age-at-first use, and talc-years of use were not significantly different among women who had also douched and those who had not (see Table 3 footnote).

Table 4 examines risk for EOC overall and for specific histologic types of ovarian cancer in four mutually exclusive usage categories: women who never douched or used talc, women who used talc but did not douche, women who douched but did not use talc, and women who both douched and used talc. Douching, compared with neither douching nor using talc, did not increase risk for EOC overall or histologic subtypes, and this was true whether the douching product was store-bought or homemade.

Compared with not douching or using talc, the OR for using talc was elevated for EOC overall (OR, 1.29; 95% CI, 1.10–1.51), for serous borderline tumors (OR, 1.39; 95% CI, 0.99–1.97), and for serous invasive tumors (OR, 1.39; 95% CI, 1.14–1.69). The associations were slightly stronger for women who used talc and store-bought douches, compared with those who used neither; OR, 1.53 (95% CI, 1.11–2.10) for EOC overall, OR, 2.11 (95% CI, 1.13–3.96) for serous borderline, and OR, 1.57 (95% CI, 1.07–2.31) for serous invasive tumors. Risk for the endometrioid subtype was elevated for those who used talc and store-bought douches compared with talc use without douching, but the association was not statistically significant. Although these findings are suggestive of an interaction between talc use and store-bought douches, formal tests for interaction did not reach the level of statistical significance (see Table 4 footnote).

Table 5 shows the risk for PID, ectopic pregnancy, and cervical neoplasia in cases and controls separately, again by the mutually exclusive categories related to talc and type of douche used. Relative to cases who neither douched nor used talc, elevated risks for PID were found for cases who used a store-bought douche

Table 2. Associations between douching and ovarian cancer by talc use

Douching	Controls N (%)	Cases N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	P[a]
All cases and controls					
Douched regularly					
No	1,738 (82.8)	1,683 (82.5)	1.00 (reference)	1.00 (reference)	
Yes	362 (17.2)	357 (17.5)	1.02 (0.87–1.20)	0.98 (0.83–1.17)	0.85
Age at first use, years					
<20	90 (4.3)	100 (4.9)	1.15 (0.86–1.54)	1.12 (0.82–1.52)	0.48
20–29	217 (10.4)	184 (9.0)	0.88 (0.71–1.08)	0.84 (0.68–1.05)	0.12
≥30	51 (2.4)	68 (3.3)	1.38 (0.95–1.99)	1.34 (0.91–1.97)	0.14
Duration of douching					
≤5 years	92 (4.4)	94 (4.6)	1.06 (0.79–1.42)	1.04 (0.76–1.41)	0.82
6–15 years	92 (4.4)	101 (5.0)	1.13 (0.85–1.52)	1.12 (0.83–1.52)	0.46
16–26 years	87 (4.2)	72 (3.5)	0.86 (0.62–1.18)	0.80 (0.57–1.11)	0.18
>26 years	87 (4.2)	84 (4.1)	1.00 (0.73–1.36)	0.93 (0.67–1.29)	0.68
P_{trend}					0.50
Type of douche used					
Store-bought	217 (10.3)	239 (11.7)	1.14 (0.94–1.38)	1.11 (0.91–1.37)	0.30
Homemade	142 (6.8)	114 (5.6)	0.83 (0.64–1.07)	0.78 (0.60–1.02)	0.07
Among talc users					
Douched regularly[b]					
No	428 (78.0)	496 (77.3)	1.00 (reference)	1.00 (reference)	
Yes	121 (22.0)	146 (22.7)	1.04 (0.79–1.37)	1.03 (0.77–1.38)	0.84
Age at first use, years[c]					
<20	26 (4.8)	45 (7.1)	1.49 (0.91–2.46)	1.45 (0.85–2.46)	0.17
20–29	74 (13.5)	71 (11.1)	0.83 (0.58–1.18)	0.82 (0.57–1.19)	0.29
≥30	19 (3.5)	26 (4.1)	1.18 (0.64–2.16)	1.17 (0.62–2.20)	0.64
Duration of douching[d]					
≤5 years	27 (4.9)	33 (5.2)	1.05 (0.62–1.78)	1.12 (0.65–1.93)	0.68
6–15 years	32 (5.9)	43 (6.7)	1.16 (0.72–1.87)	1.18 (0.72–1.95)	0.51
16–26 years	30 (5.5)	29 (4.5)	0.83 (0.49–1.41)	0.69 (0.39–1.21)	0.20
>26 years	29 (5.3)	37 (5.8)	1.10 (0.67–1.82)	1.09 (0.64–1.87)	0.75
P_{trend}					0.91
Type of douche used[e]					
Store-bought	75 (13.7)	108 (16.9)	1.24 (0.90–1.71)	1.22 (0.87–1.71)	0.25
Homemade	45 (8.2)	35 (5.5)	0.67 (0.42–1.06)	0.67 (0.41–1.10)	0.11
Among those who never used talc					
Douched regularly[b]					
No	1,310 (84.5)	1,187 (84.9)	1.00 (reference)	1.00 (reference)	
Yes	241 (15.5)	211 (15.1)	0.97 (0.79–1.18)	0.94 (0.76–1.16)	0.58
Age at first use, years[c]					
<20	64 (4.1)	55 (3.9)	0.95 (0.66–1.37)	0.94 (0.63–1.39)	0.74
20–29	143 (9.2)	113 (8.1)	0.87 (0.67–1.13)	0.84 (0.64–1.10)	0.20
≥30	32 (2.1)	42 (3.0)	1.45 (0.91–2.31)	1.48 (0.91–2.42)	0.11
Duration of douching[d]					
≤5 years	65 (4.2)	61 (4.4)	1.04 (0.72–1.48)	1.00 (0.69–1.44)	0.98
6–15 years	60 (3.9)	58 (4.2)	1.07 (0.74–1.54)	1.08 (0.74–1.59)	0.69
16–26 years	57 (3.7)	43 (3.1)	0.83 (0.56–1.25)	0.83 (0.55–1.27)	0.40
>26 years	58 (3.7)	47 (3.4)	0.89 (0.60–1.32)	0.81 (0.54–1.24)	0.33
P_{trend}					0.33
Type of douche used[a]					
Store-bought	142 (9.2)	131 (9.4)	1.02 (0.79–1.31)	1.01 (0.78–1.32)	0.92
Homemade	97 (6.3)	79 (5.7)	0.90 (0.66–1.22)	0.85 (0.61–1.18)	0.33

NOTE: The following variables have missing data: age at first use ($n = 9$), duration ($n = 10$), and type of douche ($n = 7$).

[a]Adjusted for age, study center and phase, menopausal status, marital status, parity, oral contraceptive use and duration, tubal ligation, BMI, race, diaphragm use, spermicide use, smoking, days of menstrual flow, and age at menarche.

[b]$P_{heterogeneity} = 0.79$.

[c]$P_{heterogeneity} = 0.43$.

[d]$P_{heterogeneity} = 0.91$.

[e]$P_{heterogeneity} = 0.50$.

alone OR, 4.44 (95% CI, 1.22–16.1) and for those who used a store-bought douche and talc, OR, 5.46 (95% CI, 1.64–18.2). An elevated risk for cervical neoplasia in cases who used homemade douches was also seen. Risk estimates for these associations were imprecise as illustrated by their wide CIs. For controls, none of the ORs reached significance nor were differences in risk found by whether homemade or store-bought douches were used.

Discussion

Using data from a case–control study of ovarian cancer, we examined the role of douching as a risk factor for EOC independent of talc use and, conversely, whether talc use affects risks for adverse reproductive outcomes that have been associated with douching such as PID. Examined as separate variables, douching

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Table 3. Associations between genital talc use and ovarian cancer by douching

Genital talc use	Controls N (%)	Cases N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	P[a]
All cases and controls					
Ever used					
No	1,551 (73.9)	1,398 (68.5)	1.00 (reference)	1.00 (reference)	
Yes	549 (26.1)	642 (31.5)	1.30 (1.13–1.48)	1.30 (1.13–1.50)	0.0003
Age at first use, years					
<20	343 (16.4)	363 (17.9)	1.17 (1.00–1.38)	1.15 (0.97–1.37)	0.10
20–29	122 (5.8)	183 (9.0)	1.66 (1.31–2.12)	1.73 (1.35–2.23)	<0.0001
≥30	76 (3.6)	87 (4.3)	1.27 (0.93–1.74)	1.25 (0.90–1.74)	0.18
Talc-years					
≤1 talc-year	138 (6.6)	138 (6.8)	1.11 (0.87–1.42)	1.12 (0.86–1.45)	0.40
>1–5 talc-years	124 (5.9)	148 (7.3)	1.32 (1.03–1.70)	1.37 (1.05–1.77)	0.02
>5–24 talc-years	146 (7.0)	170 (8.4)	1.29 (1.02–1.63)	1.24 (0.97–1.58)	0.08
>26 talc-years	127 (6.1)	171 (8.4)	1.49 (1.17–1.90)	1.51 (1.17–1.95)	0.001
P_{trend}					0.0001
Among women who douched					
Ever used[b]					
No	241 (66.6)	211 (59.1)	1.00 (reference)	1.00 (reference)	
Yes	121 (33.4)	146 (40.9)	1.38 (1.02–1.87)	1.32 (0.95–1.82)	0.10
Age at first use, years[c]					
<20	80 (22.2)	85 (23.9)	1.21 (0.85–1.73)	1.15 (0.78–1.69)	0.47
20–29	25 (6.9)	45 (12.6)	2.06 (1.22–3.47)	2.04 (1.17–3.55)	0.01
≥30	14 (3.9)	15 (4.2)	1.22 (0.58–2.59)	1.19 (0.54–2.62)	0.67
Talc-years[d]					
≤1 talc-year	24 (6.7)	26 (7.3)	1.24 (0.69–2.22)	1.31 (0.69–2.47)	0.41
>1–5 talc-years	19 (5.3)	30 (8.5)	1.80 (0.99–3.30)	1.89 (1.00–3.57)	0.05
>5–24 talc-years	40 (11.1)	40 (11.3)	1.14 (0.71–1.84)	0.95 (0.57–1.59)	0.85
>26 talc-years	36 (10.0)	47 (13.3)	1.49 (0.93–2.39)	1.47 (0.90–2.43)	0.13
P_{trend}					0.15
Among women who did not douche					
Ever used[b]					
No	1,310 (75.4)	1,187 (70.5)	1.00 (reference)	1.00 (reference)	
Yes	428 (24.6)	496 (29.5)	1.28 (1.10–1.49)	1.28 (1.09–1.51)	0.002
Age at first use, years[c]					
<20	263 (15.2)	278 (16.6)	1.17 (0.97–1.41)	1.15 (0.94–1.39)	0.17
20–29	97 (5.6)	138 (8.2)	1.57 (1.20–2.06)	1.63 (1.23–2.16)	0.0007
≥30	62 (3.6)	72 (4.3)	1.28 (0.90–1.82)	1.27 (0.88–1.84)	0.19
Talc-years[d]					
≤1 talc-year	114 (6.6)	112 (6.7)	1.08 (0.83–1.42)	1.08 (0.82–1.44)	0.58
>1–5 talc-years	105 (6.1)	118 (7.1)	1.24 (0.94–1.63)	1.30 (0.98–1.73)	0.07
>5–24 talc-years	106 (6.1)	130 (7.8)	1.35 (1.04–1.77)	1.31 (0.99–1.73)	0.06
>26 talc-years	91 (5.3)	124 (7.4)	1.50 (1.13–1.99)	1.51 (1.12–2.03)	0.007
P_{trend}					0.0006

NOTE: The following variables have missing data: age at first use ($n = 17$) and talc-years ($n = 29$).

[a]Adjusted for age, study center and phase, menopausal status, marital status, parity, oral contraceptive use and duration, tubal ligation, BMI, race, diaphragm use, spermicide use, smoking, days of menstrual flow, and age at menarche.

[b]$P_{heterogeneity} = 0.79$.

[c]$P_{heterogeneity} = 0.85$.

[d]$P_{heterogeneity} = 0.76$.

was not an independent risk factor for ovarian cancer while genital talc use, with or without douching, increased the risk for ovarian cancer. Compared with women who neither douched nor used talc, elevated risks, especially for serous borderline and serous invasive cancer, were seen for women who used talc but did not douche, as well as for women who used talc and, also, douched with a store-bought product. In our analysis, we adjusted for menopausal and marital status, BMI, race, menstrual factors, and contraceptives used including tubal ligation.

The first study to address risk for ovarian cancer associated with douching was also one of the first epidemiologic studies of ovarian cancer (12). McGowan and colleagues found that women with ovarian cancer did not differ from controls in their regular use of douches, consistency of use, age began, or years of use. An early study on talc and ovarian cancer examined douching as a potential confounding factor and found adjustment for it did not

negate the talc association (13). Subsequent studies on talc and ovarian cancer did not look at douching either as a confounder or an independent risk factor for ovarian cancer, and the issue was not readdressed until the Gonzalez and colleagues' Sister Study in 2017 (11). The "Sister Study" followed sisters of women who had been diagnosed with breast cancer for new occurrence of ovarian cancer. This study reported that douching (in the previous 12 months) was associated with an OR (95% CI) risk for ovarian cancer of 1.84 (1.2–2.8) while talc use (in the previous 12 months) was not, 0.73 (0.44–1.2).

Related both to the positive finding with douching and null association with talc in the Gonzalez and colleagues study, several issues should be considered. Because more than one sister from a family could have been enrolled, the authors used a statistical technique to adjust for number of family units. It is not clear whether this technique used the actual number of family units

Table 4. Associations between douching and genital talc use and ovarian cancer by histologic type

	Never used talc or douched	Talc use, no douching	No talc use, douched			Talc use and douched		
			Any type of douche	Store-bought douche	Homemade douche	Any type of douche	Store-bought douche[a]	Homemade douche[b]
Controls								
N (%)	1,310 (62.5)	428 (20.4)	239 (11.4)	142 (6.8)	97 (4.6)	120 (5.8)	75 (3.6)	45 (2.2)
All cases								
N (%)	1,187 (58.3)	496 (24.4)	210 (10.3)	131 (6.4)	79 (3.9)	143 (7.0)	108 (5.3)	35 (1.7)
OR (95% CI)[c]	1.00 (reference)	1.29 (1.10–1.51)	0.95 (0.77–1.18)	1.02 (0.79–1.33)	0.85 (0.62–1.17)	1.27 (0.97–1.17)	1.53 (1.11–2.10)	0.83 (0.52–1.33)
P[c]		0.002	0.65	0.87	0.32	0.32	0.009	0.44
Serous borderline cases								
N (%)	149 (60.1)	57 (23.0)	26 (10.5)	18 (7.3)	8 (3.2)	16 (6.5)	15 (6.0)	1 (0.4)
OR (95% CI)[c]	1.00 (reference)	1.39 (0.99–1.97)	1.26 (0.79–2.02)	1.28 (0.74–2.22)	1.22 (0.56–2.65)	1.52 (0.84–2.75)	2.11 (1.13–3.96)	0.28 (0.04–2.18)
P[c]		0.06	0.33	0.38	0.62	0.17	0.02	0.23
Serous invasive cases								
N (%)	521 (54.0)	256 (26.5)	109 (11.3)	66 (6.8)	43 (4.5)	79 (8.2)	53 (5.5)	26 (2.7)
OR (95% CI)[c]	1.00 (reference)	1.39 (1.14–1.69)	0.96 (0.74–1.24)	1.11 (0.81–1.54)	0.77 (0.52–1.14)	1.40 (1.02–1.92)	1.57 (1.07–2.31)	1.12 (0.67–1.88)
P[c]		0.001	0.75	0.51	0.19	0.04	0.02	0.67
Mucinous								
N (%)	167 (69.0)	45 (18.6)	21 (8.7)	15 (6.2)	6 (2.5)	9 (3.7)	6 (2.5)	3 (1.2)
OR (95% CI)[c]	1.00 (reference)	0.97 (0.68–1.40)	0.84 (0.51–1.39)	0.91 (0.50–1.63)	0.72 (0.30–1.72)	0.64 (0.31–1.35)	0.62 (0.25–1.54)	0.68 (0.20–2.31)
P[c]		0.89	0.50	0.74	0.46	0.24	0.30	0.54
Endometrioid								
N (%)	201 (60.7)	85 (25.7)	22 (6.6)	15 (4.5)	7 (2.1)	23 (6.9)	18 (5.4)	5 (1.5)
OR (95% CI)[c]	1.00 (reference)	1.26 (0.94–1.69)	0.67 (0.41–1.10)	0.71 (0.40–1.26)	0.61 (0.27–1.38)	1.40 (0.85–2.32)	1.74 (0.98–3.09)	0.82 (0.31–2.18)
P[c]		0.13	0.11	0.24	0.24	0.19	0.06	0.69
Clear cell								
N (%)	74 (63.8)	25 (21.6)	11 (9.5)	7 (6.0)	4 (3.4)	6 (5.2)	6 (5.2)	0 (0)
OR (95% CI)[c]	1.00 (reference)	1.08 (0.66–1.78)	0.99 (0.50–1.95)	1.04 (0.46–2.39)	0.88 (0.30–2.60)	0.96 (0.39–2.36)	1.47 (0.58–3.70)	—
P[c]		0.76	0.97	0.92	0.82	0.93	0.41	—

[a]P value comparing talc use (no douching) versus talc use (and douching with store-bought product): all, P = 0.32; serous borderline, P = 0.21; serous invasive, P = 0.54; mucinous, P = 0.35; endometrioid, P = 0.29; and clear cell, P = 0.54.

[b]P value comparing talc use (no douching) versus talc use (and douching with homemade product): all, P = 0.07; serous borderline, P = 0.13; serous invasive, P = 0.4; mucinous, P = 0.58; and endometrioid, P = 0.40.

[c]Adjusted for age, study center and phase, menopausal status, marital status, parity, oral contraceptive use and duration, tubal ligation, BMI, race, diaphragm use, spermicide use, smoking, days of menstrual flow, and age at menarche.

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Table 5. Adverse reproductive outcomes among ovarian cancer cases and controls

	Cases					Controls				
	No N (%)	Yes N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	P[a]	No N (%)	Yes N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	P[a]
Outcome: PID[b]										
Never used talc or douched	450 (56.5)	11 (39.3)	1.00 (reference)	1.00 (reference)		511 (61.2)	12 (63.2)	1.00 (reference)	1.00 (reference)	
Talc use, no douching	214 (26.9)	7 (25.0)	1.34 (0.51–3.50)	1.41 (0.52–3.83)	0.50	192 (23.0)	7 (36.8)	1.55 (0.60–4.00)	1.70 (0.62–4.66)	0.30
Douched (store-bought), no talc use	50 (6.3)	4 (14.3)	3.27 (1.00–10.7)	4.44 (1.22–16.1)	0.02	49 (5.9)	0 (0)	—	—	—
Douched (homemade), no talc use	27 (3.4)	0 (0)	—	—	—	27 (3.2)	0 (0)	—	—	—
Both talc and douche (store-bought) use	41 (5.1)	5 (17.9)	4.99 (1.65–15.0)	5.46 (1.64–18.2)	0.006	37 (4.4)	0 (0)	—	—	—
Both talc and douche (homemade) use	15 (1.9)	1 (3.6)	2.73 (0.33–22.5)	3.62 (0.36–36.0)	0.27	19 (2.3)	0 (0)	—	—	—
Outcome: ectopic pregnancy[c]										
Never used talc or douched	841 (55.9)	14 (56.0)	1.00 (reference)	1.00 (reference)		1,091 (61.3)	26 (66.7)	1.00 (reference)	1.00 (reference)	
Talc use, no douching	367 (24.4)	6 (24.0)	0.99 (0.38–2.58)	1.14 (0.42–3.10)	0.80	363 (20.4)	7 (17.9)	0.81 (0.35–1.89)	0.90 (0.38–2.13)	0.80
Douched (store-bought), no talc use	105 (7.0)	3 (12.0)	1.72 (0.49–6.09)	2.02 (0.51–7.96)	0.32	130 (7.3)	2 (5.1)	0.65 (0.15–2.76)	0.68 (0.16–2.98)	0.61
Douched (homemade), no talc use	74 (4.9)	0 (0)	—	—	—	92 (5.2)	1 (2.6)	0.46 (0.06–3.41)	0.52 (0.07–4.07)	0.53
Both talc and douche (store-bought) use	87 (5.8)	2 (8.0)	1.39 (0.31–6.20)	2.08 (0.43–10.1)	0.36	64 (3.6)	3 (7.7)	1.97 (0.58–6.69)	2.42 (0.67–8.70)	0.18
Both talc and douche (homemade) use	30 (2.0)	0 (0)	—	—	—	41 (2.3)	0 (0)	—	—	—
Outcome: cervical neoplasia[d]										
Never used talc or douched	797 (57.0)	45 (53.6)	1.00 (reference)	1.00 (reference)		904 (61.1)	53 (54.6)	1.00 (reference)	1.00 (reference)	
Talc use, no douching	361 (25.8)	20 (23.8)	0.98 (0.57–1.69)	1.05 (0.60–1.82)	0.88	333 (22.5)	29 (29.9)	1.49 (0.93–2.38)	1.50 (0.92–2.46)	0.10
Douched (store-bought), no talc use	92 (6.6)	4 (4.8)	0.77 (0.27–2.19)	0.83 (0.28–2.42)	0.73	103 (7.0)	5 (5.2)	0.83 (0.32–2.12)	0.88 (0.33–2.32)	0.80
Douched (homemade), no talc use	47 (3.4)	5 (6.0)	1.88 (0.71–4.97)	3.28 (1.17–9.22)	0.02	51 (3.4)	4 (4.1)	1.34 (0.47–3.85)	1.58 (0.53–4.77)	0.41
Both talc and douche (store-bought) use	77 (5.5)	8 (9.5)	1.84 (0.84–4.04)	1.94 (0.85–4.43)	0.12	57 (3.9)	5 (5.2)	1.50 (0.58–3.89)	1.40 (0.51–3.82)	0.52
Both talc and douche (homemade) use	25 (1.8)	2 (2.4)	1.42 (0.33–6.17)	1.88 (0.41–8.64)	0.41	32 (2.2)	1 (1.0)	0.53 (0.07–3.98)	0.45 (0.06–3.49)	0.44

[a]Adjusted for age, study center and phase, parity, oral contraceptive use and duration, tubal ligation, BMI, race, diaphragm use, spermicide use, menopausal status, and smoking.
[b]Study phase III only.
[c]Among those ever pregnant.
[d]Study phases II–III only.

which, ideally, should have been explicitly shown in their Table 1. This is important, because 69% of women in a survey related to douching said they learned the habit from a mother or sister (3). Any genital exposure to talc in the prior year was defined by aggregating several types of exposure including use on sanitary napkins or barrier contraceptive devices. This is problematic because these types of talc exposures would not pertain to the 69% of postmenopausal cases in the study. Also, not counted would be those who had recently discontinued talc use (perhaps because of recent publicity regarding talc use and ovarian cancer association). In fact, only 14% of the cohort reported genital talc exposure in this study, far lower than the other two cohort studies, 40.4% in the Nurses' Health Study (14) and 52.6% in the Women's Health Initiative (15). Finally, an OR of 0.73 for ovarian cancer with talc reported from the Sister Study stands out as the clearest outlier in a recent meta-analysis of studies on talc and ovarian cancer (16).

Among the 362 (17.2%) controls in our study who reported regular douching, 106 (28.5%) said they used homemade vinegar and water and 25 (6.7%) used tap water, leaving about 65% who used store-bought products, with Massengill and Summer's Eve most commonly reported. However, within specific brands, multiple products are offered (e.g., medicated douches, cleansing douches, vinegar and water, and douches with different fragrances, etc.). This level of detail was not obtained in our study so the only distinction we could make was store-bought versus homemade. Notably the combination of talc-use and douching with a homemade product was associated with a reduced risk for ovarian cancer, while douching with a store-bought product with a nonsignificantly elevated risk (Table 2). In addition, compared with women who neither douched nor used talc and women who both used talc and store-bought douches had modestly higher risks for ovarian cancer overall and borderline and invasive serous cancer compared with those who used talc but did not douche. However, this apparent interaction did not reach statistical significance. No interaction between douching and talc use was seen in the Sister Study but they did not report information on type of douching product used, even at the level of store-bought or homemade.

Chemicals used in commercial douching products include emulsifiers and surfactant cleansers like octoxynol-9 and preservatives like sodium benzoate, methylchloroisothiazolinone, and citric acid, and "fragrances" which could include any of thousands of amines, aromatics, esters, and terpenes. It is likely that most of these chemicals would be capable of absorption through the vaginal mucosa. This is certainly true for the preservatives used in douches, which are capable of causing sensitization and allergic reactions (17). Pointing to a study which found women who douched had higher levels of urinary metabolites of phthalates (18), Gonzalez and colleagues suggested this may be the agent that explains why douching may increase the risk for ovarian cancer. Presence of phthalates in douches was assumed because phthalates may be used as carrier molecule for fragrances (18); but douches have not been specifically examined in studies that measured phthalates in a wide variety of personal care products (19–22). While our data cannot point to specific agents that might account for possible differences in risk for ovarian cancer between store-bought and homemade douches, the fact that differences between the two have been described for risk of other adverse reproductive health events (4, 5, 9) suggests this is likely to be a meaningful dichotomy.

In this study, we also had the opportunity to look at whether talc use can increase the risk for events that have been associated with douching including PID, ectopic pregnancy, or cervical neoplasia. In controls, neither douching nor talc use nor their combination was found to affect risks for these adverse outcomes. However, cases who douched with a store-bought product had an elevated risk for PID, regardless of whether they used talc. Furthermore, risk for cervical neoplasia was increased by use of homemade douches. Chance must be considered as an explanation for all these associations. A major limitation associated with this aim of our study is the fact that adverse events, other than ovarian cancer, were not the specific focus of our study, but collected as part of the participants' health histories. Thus, our study was not powered to detect the associations examined here with any set level of confidence. In addition, for the non-ovarian cancer adverse events, only the ever-never association could be examined. Dose-related information on douching or talc use could not be used because these had been censored on the date of the ovarian cancer diagnosis or interview and not on the date when the other adverse event occurred. This issue also affects how to deal with closure of the female tract by tubal ligation (or hysterectomy) where some might advocate truncating the exposure for age as closure as we did for talc (10). However, exclusion of women with tubal ligation did not alter key results from Tables 2 and 3. Finally, a more general concern in case–control studies is the issue of recall bias. We previously addressed this issue in our 2016 article and pointed out several arguments against recall bias as an explanation including: no association with non-genital talc use or starch-based products, variation in risk by histologic type of ovarian cancer, and stronger association with regular use than ever-use (10).

In conclusion, our study found that douching is not an independent risk factor for ovarian cancer nor did it raise the risk for EOC beyond that for talc use alone. However, there was suggestive evidence that the combination of talc and store-bought douches may add to the risks from talc use alone. A distinction between store-bought and homemade douches suggests a possible role for chemicals used in commercial douching products. Reexamination of existing studies that have information on both variables would be helpful in verifying the associations described here. Important and relevant information may also come from *in vitro* and *in vivo* studies, which look at the combined effects of talc and the chemicals found in douching products as they may affect ovarian or tubal inflammation.

Disclosure of Potential Conflicts of Interest

Authors' Contributions

Conception and design: I.M. Gabriel, L. Titus, D.W. Cramer
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.R. Welch, L. Titus, D.W. Cramer
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.F. Vitonis, D.W. Cramer
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.F. Vitonis, L. Titus
Study supervision: L. Titus

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